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Time Dependent Density Functional Response Theory Calculation of Optical Rotation as a Method for the Assignment of Absolute Configuration of Camphor-Derived Furyl Hydroperoxide and Alcohol

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The absolute configuration of (*R*)-(+)-camphor-derived furyl hydroperoxide and alcohol, which exhibit a number of stable conformations, has been successfully accomplished on the basis of time dependent density functional response theory (TDDFT) calculations of optical rotation. Assuming standard approximations, it has been found that the results are improved by using populations for the conformers derived from free energy differences instead of the commonly used PES minimum differences. This represents the first computational study devoted to the direct determination of absolute configuration of an optically pure hydroperoxide, without any need of its further chemical derivatization.

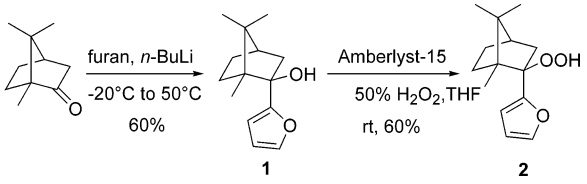
1. Introduction

In principle, the absolute configuration (AC) of a chiral molecule can be assigned by comparing the experimental and computed specific rotation at one or more frequencies in the transparent spectral region. According to the general methodology, [α] at the working frequencies is calculated for both possible ACs; then the result is compared to the experimental value, and the AC giving the closest agreement to experiment will be the correct AC.[1] This approach for the AC assignment has received in the past few years a revival of attention mainly because of the development of reliable procedures of calculation for the prediction of accurate optical rotations. Historically, Hartree−Fock (HF) based methods[2] have been the first to be developed and applied to the study of a variety of rigid and flexible molecules.[3,4] Nowadays, more reliable methodologies of calculation have been introduced, on the basis of density functional theory (DFT)[5,6] and the coupled-cluster (CC) method.[7] However, much of the literature relative to these recent methods concerns the study of rigid molecules, and few examples[8] are available regarding the case of flexible molecules exhibiting a number of stable conformations.

In connection with investigations devoted to the synthesis of racemic[9] and enantiopure[10] hydroperoxides to be used in asymmetric oxidations,[9−11] it has been recently shown that tertiary enantiopure furyl hydroperoxide **2**, i.e., (1*R*,2*R*,4*R*)-**2**, can be efficiently obtained by the two-steps sequence depicted in Scheme 1. Treatment of easily available (*R*)−(+)-camphor with 2-furyllithium in THF gave almost exclusively (1*R*,2*R*,4*R*)-**1** (*exo/endo* 97/3), which was smoothly converted into diastereoisomerically pure hydroperoxide **2** by reaction with hydrogen peroxide in acidic medium.[10]

The stereochemistry of the new generated asymmetric carbon 2 in the bicyclic skeleton of the oxidant **2** has been assigned by NOESY experiment on the alcohol derived from **2** after reduction with Ph_3P, a process known to proceed by retention of configuration.[12] Absolute configuration of optically pure secondary[13] hydroperoxides have been previously determined[14] by exciton-coupled circular dichroism (ECCD).[15] It has to be noted that this methodology requires reduction of hydroperoxide to alcohol, which is then converted into the corresponding benzoate or naphthoate derivative. To the best of our knowledge, up to now, no direct determination of the absolute configuration of tertiary enantiopure hydroperoxides has been developed either by experimental or theorethical methods. In consideration of the growing interest toward the synthesis and employment of optically pure alkyl hydroperoxides,[16] the development of a simple and straightforward way to determine their absolute configuration is highly desirable.

SCHEME 1: Two-Step Route to Camphor-Derived Furyl Hydroperoxide 2



Chiral compounds **1** and **2** are of interest as they represent two new cases of study for the recently suggested computational protocol for the assignment of the absolute configuration of molecules exhibiting several stable conformations.[8] Moreover, as far as we know, the use of the free energy for determining the conformational populations for the prediction of the optical rotation of flexible molecules has not yet been fully explored. Then, as a second goal, this paper is aimed at providing further evidence in favor of the theoretical procedure proposed for the AC assignment and at showing, at least for the molecules here considered, that the use of free energy differences for the determination of populations of the various conformers of a flexible molecule may improve the agreement with the experimental results.

2. Experimental Section

Hexane and chloroform were purchased by Aldrich. UV and CD spectra of diastereoisomerically pure (1*R*,2*R*,4*R*)-2-*exo*-hydroxy-2-*endo*-(2-furyl)-1,7,7-trimethylbicyclo[2.2.1]heptane (**1**) and (1*R*,2*R*,4*R*)-2-*exo*-hydroperoxy-2-*endo*-(2-furyl)-1,7,7-trimeth-

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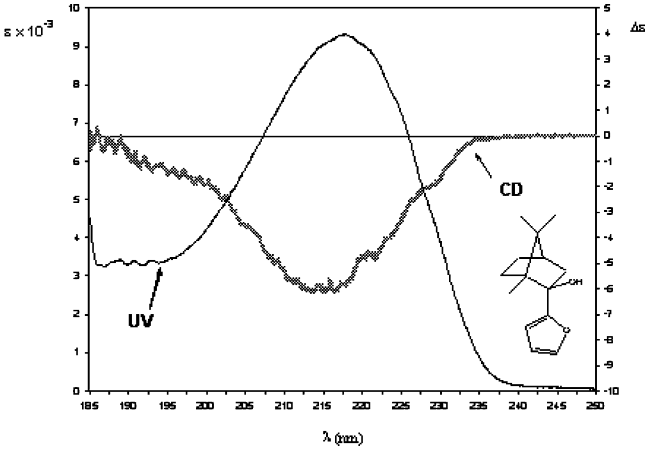

Figure 1. CD and UV spectra of a hexane solution of alcohol (1*R*,2*R*,4*R*)-**1** (c = 0.85 g/100 mL).

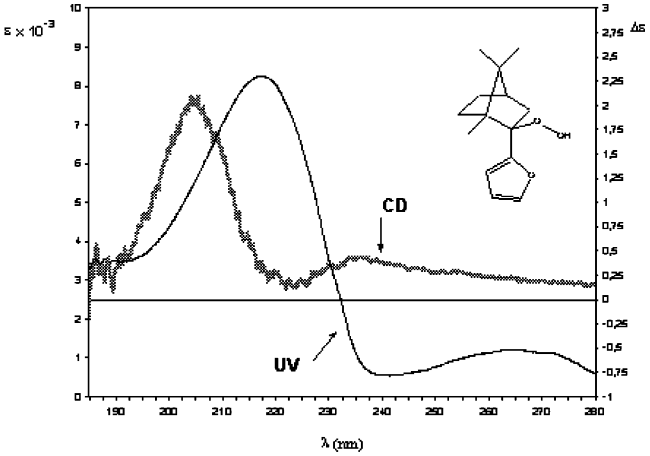

Figure 2. CD and UV spectra of a hexane solution of hydroperoxide (1*R*,2*R*,4*R*)-**2** (c = 0.85 g/100 mL).

TABLE 1: Specific Rotations at Different Concentrations for (1*R*,2*R*,4*R*)-1 and (1*R*,2*R*,4*R*)-2 in Chloroform and Hexane[a]

$[\alpha]_D^{25}$ of (1*R*,2*R*,4*R*)-**1**		$[\alpha]_D^{25}$ of (1*R*,2*R*,4*R*)-**2**	
in chloroform	in hexane	in chloroform	in hexane
−39.4 (c 1.58)	−34.1 (c 0.85)	−50.4 (c 1.00)	−65.0 (c 0.85)
−29.4 (c 0.80)	−28.6 (c 0.50)	−50.3 (c 0.50)	−65.9 (c 0.50)
−27.8 (c 0.30)	−28.3 (c 0.25)	−50.0 (c 0.25)	−63.8 (c 0.25)
−26.7 (c 0.12)	−26.8 (c 0.11)	−50.5 (c 0.10)	−62.1 (c 0.1)
−27.2 (dil ∞)	−27.4 (dil ∞)	−50.3 (dil ∞)	−60.1 (dil ∞)

[a] The specific rotations are in deg [dm(g/cm^3)]$^{-1}$, the concentrations c are in g/100 mL.

ylbicyclo[2.2.1]heptane (**2**) were recorded in hexane solution on a JASCO J-600 spectropolarimeter at 25 °C. The spectra are reported in Figures 1 and 2.

The contribution of these CD bands to $[\alpha]_D$ is easily worked out by means of the simple formulas for Kronig−Kramers transforms reported by Moscowitz.[17] For the alcohol the contribution turns out to be −83.3, whereas the two bands of the hydroperoxide give a contribution of +22.2 (15.8 + 6.4). The experimental specific rotations, at the sodium D line under ambient temperature measured for the same solutions used to record the CD spectra (see first row of the following Table 1) are −34.1 and −65.0 for (1*R*,2*R*,4*R*)-**1** and (1*R*,2*R*,4*R*)-**2** respectively. It is interesting to observe the inversion of sign for the hydroperoxide.

Specific rotations, at the sodium D line and room temperature, have been measured in hexane and chloroform at different concentrations, by means of a JASCO DIP-1000 digital polarimeter. The results are collected in Table 1, which also reports the extrapolation at infinite dilution, i.e., the intrinsic rotation,[1] in both solvents.

In the case of alcohol, it can be noticed that: (i) almost no solvent−solute effect is observed, as the intrinsic rotations converge to the same value; (ii) a nonlinear variation of the specific rotations with increasing dilution is detected, which may indicate the presence of solute−solute interactions (aggregation). In the case of hydroperoxide, the specific rotations at any dilution depend on solvent. In particular the specific rotation in chloroform remains more or less constant with dilution, suggesting a negligible interaction among the solute molecules, while in apolar hexane the trend of $[\alpha]_D$ with concentration could indicate a certain degree of aggregation for the hydroperoxide molecules.

3. Optical Rotation Calculations

According to Stephens et al.,[8] the specific rotation at a wavelength λ of the incident radiation of a macroscopic sample of a chiral molecule exhibiting n stable conformations is

$$[\alpha]_\lambda = \left[\frac{\mathrm{ee(E_1)}}{100}\right]\sum_i x_i\,[\alpha]_{\lambda,i}(\mathrm{E_1}) \qquad (1)$$

where ee(E$_1$) is the percentage enantiomeric excess of the enantiomer E$_1$, x_i is the fractional population of conformer i, and $[\alpha]_{\lambda,i}(\mathrm{E_1})$ is the specific rotation of conformer i of enantiomer E$_1$ at wavelength λ. Hence, in the case of known enantiomeric excess, the knowledge of the conformational structures and populations as well as of the specific rotations $[\alpha]_{\lambda,i}(\mathrm{E_1})$ is required to make useful predictions. The calculation of the optical rotation for each conformer i at a wavelength in the transparent spectral region is carried out by means of the molecular parameter β,[18] which is directly connected to the trace of the frequency dependent electric dipole-magnetic dipole polarizability tensor **G′**, i.e.

$$[\alpha]_{\lambda,i} = 1.34229 \times 10^{-4}\beta\bar{\nu}^2(n^2 + 2)/3M \qquad (2)$$

$$\beta = -\frac{1}{3\omega}\mathrm{Tr}[\mathbf{G}'(\omega)] \qquad (3)$$

$$\mathbf{G}'(\omega) = -\frac{4\pi}{h}\sum_{j\neq 0}\frac{\omega}{\omega_j^{\,2} - \omega^2}(\langle 0|\boldsymbol{\mu}|j\rangle\langle j|\mathbf{m}|0\rangle) \qquad (4)$$

where the angular frequency $\omega = 2\pi\nu = 2\pi c/\lambda = 2\pi c\bar{\nu}$; the specific rotation is in units of deg [dm(g/cm^3)]$^{-1}$, β is in units of (bohr)^4, the radiation wavenumber is in cm^{-1}; n is the refractive index of the medium, M is the molar mass in g/mol;ω_j is the transition frequency from ground state $|0\rangle$ to excited state $|j\rangle$, $\boldsymbol{\mu}$ and **m** are the electric and magnetic dipole operators, respectively. Indeed, **G′** depends on the conformational structure.

It is recognized by some authors[5a,7b,19] that at the sodium D line, β is in general a small quantity as two of the diagonal components of **G′** almost cancel the third one. As a consequence, even small changes in the electronic distribution may produce rather large contributions to the computed optical rotation value. Such changes may be induced by several factors as, for example, the choice of basis set, electron correlation, solvent effect, equilibrium geometry, vibrational contributions, and last but not least, the effect of dispersion passing from a static to a dynamic approach. All these effects have been deeply explored and found to be very significant,[5−7,19,20] also sometime cooperating to give fortuitous cancellation of errors. Currently, there seems to be a general agreement on the computational requirements needed for reliable optical rotation predictions,[5−7] i.e., the use of a dynamic method together with a proper treatment of the electron correlation and the use of large basis sets containing diffuse functions. Considering the CD spectra of Figures 1 and 2, the simplified computational approach recently reported[21] cannot be used.

In the following we will present calculations of optical rotation carried out by means of state-of-the-art time dependent density functional response theory (TDDFT)[5,6] for the dipole length formalism, as implemented within the TURBOMOLE package,[22] using the B3LYP functional.[5,6] London orbitals, i.e., gauge including atomic orbital (GIAO), are not supported within the TURBOMOLE package and, as a consequence, the results turn out to be dependent on gauge origin. Within TURBOMOLE the origin dependence is removed by using the dipole velocity formalism, which allows only pure DFT functionals. However, pure functionals provide less accurate results for the $\mathbf{G}'$ tensor than hybrid functionals such as B3LYP.[6b] To reduce the origin dependence of the computed optical rotations, some care has been paid to the basis set choice. It is very well known[23] that in a translation of the coordinate frame origin, $\mathbf{r}'' = \mathbf{r}' + \mathbf{d}$, the $\mathbf{G}'$ tensor changes according to

$$G'_{\alpha\beta}(r'') = G'_{\alpha\beta}(r') - \frac{\omega}{2c}\epsilon_{\beta\gamma\delta}\, d_{\delta}\, \alpha_{\alpha\gamma} \qquad (5)$$

where $\boldsymbol{\alpha}$ is the electric polarizability in the mixed length−velocity formalism, and $\beta(\mathbf{r}'') = \beta(\mathbf{r}')$ as far as $\boldsymbol{\alpha}$ is a symmetric tensor, which is true only in the limit of a complete basis set calculation. Conversely, within the algebraic approximation, the mixed length−velocity polarizability turns out to be an asymmetric tensor and the calculated optical rotations are origin dependent. This difficulty is usually removed by adopting either London orbital basis sets or the dipole velocity formalism. However, a heavy basis set dependence of the results remains. In light of eq 5, it can be seen that one way to reduce both the basis set and gauge origin dependencies, and concurrently to improve the computed optical rotations, would be to chose a basis set designed to provide optimum molecular electric polarizabilities. The polarizability consistent Sadlej basis set[24] is one of these. It is a (10s6p4d/6s4p) set of primitive Gaussian functions contracted to [5s3p2d/3s2p] according to the scheme (52111/411/22//411/22), and, actually, it has been found to provide optical rotations as accurate as those resulting by employing a much larger basis set,[25] for example, the aug-cc-pVTZ. Therefore, the Sadlej basis set has been here adopted. For the results reported hereafter, the gauge origin has been chosen to be in the molecular center of mass and, in accordance with the good performance of basis set, the origin dependence of the results has been found small, i.e., about 8% in average moving the origin from the center of mass to carbons C1 and C2 of camphor and on the oxygen of the hydroxyl group. As has been clearly demonstred,[5b,20b] the Lorentz effective field correction leads to very inaccurate results. Moreover, a methodology does not yet exist which predicts the solvent effects with uniform reliability.[20b] Therefore, solvent effects and Lorentz effective field correction have been ignored. Because, as in particular in our case, vibrational contributions to optical rotation cannot be easily determined, they have not been considered. However, for the extra effort required to calculate the vibrational frequencies needed to obtain free energy populations, a little care has been paid by choosing a basis set containing polarization functions even on hydrogens, keeping the calculation at a feasible level.

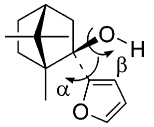

Figure 3. Scheme of the dihedral angles used for the PES scan of (1*R*,2*R*,4*R*)-**1**: α ≡ C1−C2−C−O, *β* ≡ C1−C2−O−H, where C1 and C2 are on the camphor skeleton and numerated according to IUPAC.

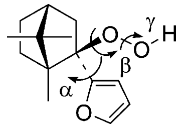

Figure 4. Scheme of the dihedral angles used for the PES scan of (1*R*,2*R*,4*R*)-**2**: α ≡ C1−C2−C−O, *β* ≡ C1−C2−O−O, *γ* ≡ C2−O−O−H, where C1 and C2 are on the camphor skeleton and numerated according to IUPAC.

4. Results and Discussion

The flexibility of both molecules has been investigated by means of HF/6-31G* PES (potential energy surface) scans with respect to the orientations of the OH, OOH, and furyl groups, as the camphor structure remains substantially unchanged; see Figures 3 and 4 for the definition of the dihedral angles employed in the search.

For each found conformer, the molecular geometry has been successively re-optimized at the DFT/B3LYP/6-31G** level of theory using the Gaussian 98 package.[26] In this way, six distinct conformers (**a**−**f**) have been found for both (1*R*,2*R*,4*R*)-**1** and (1*R*,2*R*,4*R*)-**2**, confirmed to be true PES minima being all computed vibrational frequencies real quantities.

Table 2 collects the results obtained for the alcohol and, in a similar fashion, Table 3 collects the results relative to the hydroperoxide. For each conformer, the calculated energy, free energy, population worked out for both energy and free energy differences and $[\alpha]_{\mathrm{D},i}$ are reported.

As can be observed, (1*R*,2*R*,4*R*)-**1** and (1*R*,2*R*,4*R*)-**2** present two conformers, **a** and **b**, which are predominant in terms of population and are characterized by quite similar orientation of the furyl group with respect to the camphor skeleton; see the values of dihedral angle α. In the case of the alcohol also conformers **c** and **d** present not negligible populations. The computed values of specific rotation (last column of Tables 2 and 3) change greatly, passing form one conformation to another; hence the final results will depend strongly on the chosen population values.

Looking at the predicted specific rotations collected in Table 4, one can see that the results obtained by averaging the optical rotations of the various conformers using populations calculated from energy differences (column 2) are correct in sign but present appreciable deviations from the experimental data going from 15° for the alcohol to 20−30° for the hydroperoxide. These result are within the intrinsic error of the calculational methodology, which is ca. 20−30° for$[\alpha]_{\mathrm{D}}$.[5b] However, the results obtained using populations worked out from free energy differences (column 3) are in better agreement with the experimental data. In this case the deviations from the intrinsic rotations are 4 and 0.2−10°, respectively. Returning to Tables 2 and 3, it can be noticed that, for both molecules, passing from energy to free energy, the population of conformer **a** decreases and that of **b** increases. Interesting enough, in the case of the alcohol, the calculation provides an inversion of population, **b**

TABLE 2: Structures, Energies, Free Energies, Populations and $[\alpha]_{D,i}$ of the Various Stable Conformers Found for (1*R*,2*R*,4*R*)-1

conformer	α^a	β^a	ΔE^b	$\Delta G^{b,c}$	$x(\Delta E)^d$	$X(\Delta G)^e$	$[\alpha]_{D,i}{}^f$
a	90.0	176.2	0.000000	0.000000	51.66	43.03	56.4
b	−72.1	79.2	0.146097	−0.030748	40.37	45.33	−91.9
c	−61.7	173.3	1.388323	1.132027	4.96	6.37	−105.1
d	79.4	54.0	1.875253	1.371736	2.18	4.25	28.9
e	87.7	−36.5	2.507986	2.344376	0.79	0.91	18.6
f	−61.7	−26.4	3.881924	3.188376	0.07	0.20	−117.5

[a] DFT/B3LYP/6-31G** dihedral angles in deg, for definition, see Figure 3. [b] In kcal/mol. [c] At 298.15 K including the zero-order energy correction. [d] Percentage populations obtained from ΔE values using the Boltzmann statistics. [e] Percentage populations obtained from ΔG values using the Boltzmann statistics. [f] In deg $[\mathrm{dm(g/cm^3)}]^{-1}$, calculated at TDDFT/B3LYP level of theory adopting the polarizability consistent Sadlej basis set, neglecting solvent and vibrational effects.

TABLE 3: Structures, Energies, Free Energies, Populations and $[\alpha]_{D,i}$ of the Various Stable Conformers Found for (1*R*,2*R*,4*R*)-2

conformer	α^a	β^a	γ^a	ΔE^b	$\Delta G^{b,c}$	$x(\Delta E)^d$	$x(\Delta G)^e$	$[\alpha]_{D,i}{}^f$
a	97.1	−169.1	−79.9	0.000000	0.000000	85.98	60.52	−19.5
b	−72.3	−174.6	−96.6	1.107786	0.281752	13.25	37.62	−106.5
c	116.8	72.5	90.0	3.156715	2.405872	0.42	1.04	97.9
d	−35.6	77.0	95.1	3.354140	2.630520	0.30	0.71	108.2
e	−39.2	82.8	−101.4	4.650866	4.022336	0.03	0.07	−21.1
f	101.6	72.8	−110.7	4.973033	4.437120	0.02	0.03	−41.4

[a] DFT/B3LYP/6-31G** dihedral angles in deg, for definition, see Figure 4. [b] In kcal/mol. [c] At 298.15 K including the zero-order energy correction. [d] Percentage populations obtained from ΔE values using the Boltzmann statistics. [e] Percentage populations obtained from ΔG values using the Boltzmann statistics. [f] In deg $[\mathrm{dm(g/cm^3)}]^{-1}$, calculated at TDDFT/B3LYP level of theory adopting the polarizability consistent Sadlej basis set, neglecting solvent and vibrational effects.

TABLE 4: Calculated Specific Rotations and Experimental Intrinsic Rotations in deg $[\mathrm{dm(g/cm^3)}]^{-1}$ of (1*R*,2*R*,4*R*)-1 and (1*R*,2*R*,4*R*)-2

molecule	$[\alpha]_D$ (energy pops)^a	$[\alpha]_D$ (free energy pops)^b	$[\alpha]_D$ (exp)^c	$[\alpha]_D$ (exp)^d
(1*R*,2*R*,4*R*)-**1**	−12.4	−22.7	−27.2	−27.4
(1*R*,2*R*,4*R*)-**2**	−30.2	−50.1	−50.3	−60.1

[a] Conformational average obtained using populations calculated from ΔE values. [b] Conformational average obtained using populations calculated from ΔG values at 298.15 K. [c] Intrinsic rotation in chloroform under ambient temperature, this work. [d] Intrinsic rotation in hexane under ambient temperature, this work.

being a little more stable than **a** in terms of free energy. As the specific rotation of conformer **b** of both molecules is largely negative, the predictions for $[\alpha]_D$ obtained using populations derived from free energy differences are more negative and closer to experimental values.

An interpretation of this result can be given, for both molecules, in terms of vibration, translational and rotational contributions to free energy being almost the same for all conformations. The calculation shows that the zero-point energy does not contribute to the difference of stability between **a** and **b**, whereas a negative contribution to ΔG comes almost exclusively from the entropic term, which makes plausible the idea of a larger number of vibrational states available for conformer **b** with respect to conformer **a**. This has evidence in the fact that, for both molecules, many vibrational frequencies of **b**, in particular the lowest ones, have been found smaller than those of **a**.

In conclusion, the specific rotations calculated for (1*R*,2*R*,4*R*)-**1** and (1*R*,2*R*,4*R*)-**2** match quite nicely the experimental data, therefore confirming the assignment of the absolute configuration previously obtained. The match seems to be improved by using populations derived from free energy. However, it should be remarked that (i) energy and free energy differences rely on approximate theory; (ii) solvent and vibrational effects have not been included. Then, before this result is transformed in a rule of calculation, the study of further cases must be undertaken to provide statistical significance to the method.

5. Conclusions

In the present paper, on the basis of TDDFT calculation of optical rotation, it has been demonstrated, for the first time, the possibility of determining the absolute configuration of a tertiary enantiopure hydroperoxide by knowing its optical rotation, without the need of further chemical derivatization. In consideration of the growing interest in the synthesis and use of optically pure alkyl hydroperoxides in asymmetric oxidations, a direct method for the determination of absolute configuration can be useful and an alternative to experimental methodologies. The results obtained confirm the reliability of the computational protocol suggested by Stephens et al.[8] for the treatment of flexible molecules exhibiting several stable conformations. Moreover, using populations worked out from free energy differences, an excellent agreement with the experimental data of optical rotation is achieved, thus stimulating their employment instead of the commonly used PES minimum differences.

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